The Rejection of Claims 21, 22, 27, and 28 Under 35 U.S.C. § 251

Claims 21, 22, 27, and 28 are rejected under 35 U.S.C. § 251 for improperly attempting to recapture subject matter surrendered in the application for the patent upon which the present reissue is based. Applicants respectfully traverse.

The Office Action asserts that claims 21, 22, 27, and 28 improperly attempt to recapture subject matter surrendered during the prosecution of the applications that eventually issued into U.S. Patent 5,840,531 because they recite "a portion." The Office Action alleges that "claims 21.21.27 and 28 [sic] with the recitation of 'a portion' is improper recapture for broadening." (Page 4, lines 7-8.) Supporting its allegation, the Office Action states that "the office in application 08/741,096 (for which 08/909,725 claims priority) told applicant that the specification was enabled for the specific construct based on a particular sequence (with a particular numbering system) and was not enabled for expression of any INGAP activity from any source using any host organism. Note that claims 21-22 are directed to a 'portion' of the human INGAP coding sequence." (Page 15, lines 14-19.)

Claims 21, 22, 27 and 28 do not run afoul of 35 U.S.C. § 251 for a number of reasons. First, the Federal Circuit held, "The proper focus is on the *scope* of the claims, not on the individual *feature* or *element* purportedly given up during prosecution of the original application." *Ball Corp. v. U.S.*, 729 F2d. 1429 (Fed. Cir. 1984). Claims 21, 22, 27 and 28 are directed to a scope which is entirely different than the claims which were rejected in the parent application. These claims are directed to different compositions of matter entirely. Claims 21-22 are directed to oligonucleotide primers and claims 27-28 are directed to methods of making expression constructs. No claims to this subject matter were previously presented. Thus there could have been no surrender of claims of this scope because they were never before presented.

Moreover, even if it were proper to focus on individual elements rather than on the claim as a whole, the claims would still not run afoul of 35 U.S.C. § 251. The Federal Circuit in *Ball, supra,* stated that "the patentee is free to acquire, through reissue, claims that are *narrower* in scope than the canceled claims. If the reissue claims are narrower than the cancelled claims, yet broader than the original patent claims, reissue must be sought within 2 years after grant of the original patent." The Office Action urges that reissue applicants are attempting to recover claims which recite undefined portions of INGAP. However, claims 21, 22, 27 and 28 do not recite undefined portions of INGAP. Claims 21, 22, 27 and 28 recite a specific portion of INGAP, *i.e.,* mature INGAP which lacks the signal sequence. The portion is not an undefined portion as allegedly was surrendered during prosecution. Thus the element which the Office Action focuses on is not of the same scope or broader than the surrendered element, but rather is narrower in reciting a single, specific portion of INGAP, *i.e.,* mature INGAP, rather than its pre-protein. Thus there is no recapture of surrendered subject matter. Withdrawal of this rejection to claims 21-22, and 27-28 is respectfully requested.

Claim Objection

Claim 49 allegedly does not comply with sequence rules. The Office Action asserts that: "Although SEQ ID NO: 2 and 3 are set forth in the sequence listing, the recited sequence in the claim is not *per se* found as a separate sequence in the sequence listing." (Page 5, lines 3-4.) The recited sequences have been deleted from claim 49 as suggested in the Office Action. Thus the alleged deficiency has been obviated. Withdrawal of the objection to claim 49 is respectfully requested.

Drawing

Applicants submit a set of formal drawings to comply with 37 CFR §1.173(a)(2).

Specification

The specification has been objected to for disclosing "INGAP protein." The Office Action asserts that "'INGAP' is sufficient as it means 'islet cell neogenesis protein.'" (Page 6, line 4.) The specification has been amended to delete "protein" from each recitation of "INGAP protein." Withdrawal of the objection is respectfully requested.

The Rejection of Claims 1-49 Under 35 U.S.C. § 112, First Paragraph

Claims 1-49 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

To determine compliance with the written description requirement, the description must clearly allow persons of ordinary skill in the art to recognize that applicants invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). See MPEP § 2163.02. The Office Action asserts three specific reasons as to why the claims lack adequate written description. Each will be discussed separately.

A. The Office Action asserts that the claims are not adequately described because they recite INGAP activity without describing the functional activity of INGAP in the specification or requiring an INGAP functional activity in the claims. The Office Action alleges that "neither the specification nor the claims describes the INGAP activity (see for example claim 1). Further, the

claims recite an islet cell neogenesis associated protein (INGAP) and the specific sequence with no limitation to the function of the protein (see claims 1, and 21)." (Page 7, lines 1-4.)

Activities of INGAP were known in the art (WO 96/26215, published August 29, 1996) and are described in the specification. The specification discloses that INGAP "is responsible for stimulating islet cell regeneration." Column 1, lines 27-28. The specification also discloses that INGAP has "the ability to induce ductal cell proliferation." Column 11, line 13. Application Ser. No. 08/709,662, incorporated by reference into the instant application at column 1, line 31, further describes biological activities of INGAP. See U.S. Patent 5,840,531 ('531 patent) granted on Ser. No. 08/709,662. The '531 patent teaches that "INGAP and fragments thereof are capable of inducing and stimulating islet cells to grow. Moreover, they are capable of inducing differentiation of pancreatic duct cells, and of allowing such cells to avoid the apoptotic pathway." Column 7, lines 44-48. "INGAP protein plays a role in stimulation of islet neogenesis, in particular, in beta cell regeneration from ductal cells." Column 12, lines 41-43. Thus the specification describes biological activities that include induction of ductal cell proliferation and differentiation, induction of beta cell regeneration from ductal cells, induction and stimulation of islet cell growth, and avoidance of apoptosis in ductal cells. These same teachings were known in the art by virtue of the publication of WO 96/2615 prior to the priority date of the subject application. Thus the functional activity of INGAP is taught and was known in the art.

The Office Action urges that although claims 1 and 21 recite specific sequences, they do not limit the function of the protein and therefore are inadequately described. This ground of rejection is respectfully traversed. The nucleotide sequences recited cause production of a particular protein which inherently has certain properties. The specification and prior art teach

those properties. There is no reason for those properties to be recited in claims 1 and 21. Claims to a nucleic acid construct and oligonucleotide primers need not recite activity of encoded proteins to demonstrate possession of the invention.

B. The Office Action also alleges that the claims lack adequate written description because "portion" is recited without being defined. The Office Action asserts that "claims 21 and 23-26 recite INGAP coding sequence and no sequence or characteristic (i.e. size/length) of the 'portion' is provided (claim 29.)" Page 7, lines 4-5. Characteristics of portions however are provided by each claim in which "portion" is recited. Independent claim 21 recites that the portion of human INGAP coding sequence "excludes the nucleotides encoding the signal peptide." Independent claim 23, from which claims 24-26 depend, recites that the coding sequence "is devoid of the signal sequence of the coding sequence of INGAP." Thus the portion of INGAP recited is a part of the whole coding sequence lacking the nucleotides encoding the signal peptide. The specification discloses that the "signal sequence comprises amino acids 1 to 26 as shown in SEQ ID NO: 5." Column 2, lines 33-34. Thus the portion recited is human INGAP sequence that lacks the nucleotides that encode amino acid residues 1 to 26 shown in SEQ ID NO: 5.

More importantly, the last clause of claim 21 recites, "[A] first of said oligonucleotide primers hybridizes to the 5' end of the coding sequence of mature human INGAP and the second of said oligonucleotide primer hybridizes to the 3' end of the coding sequence of mature human INGAP." Thus the recited portion is not any portion but a portion which is the mature human INGAP which lacks its signal sequence. The claim thus defines "portion" with total particularity and evidences applicants' possession of the invention at the time of filing. Similarly claim 23 recites a coding sequence for mature human INGAP. No undefined portions are encompassed by

this claim. One of skill in the art would understand that applicants had possession of the claimed invention with regard to the portion set forth in rejected claims 21 and 23-26.

C. The Office Action also alleges that claims 21-28 which recite "hybridizes" are not adequately described because neither the claims nor the specification sets forth the hybridization conditions to be used. Applicants respectfully submit that this ground of rejection does not apply to claims 23-28 which do not recite "hybridizes." This ground of rejection also does not apply to claim 22. Claim 22 specifies with total particularity the sequences of the primers. Thus there is no doubt what the claimed primers are or that applicants were in possession of them at the time of filing.

Claim 21 recites that the oligonucleotide primers hybridize to the 5' or 3' end of the coding sequence for mature human INGAP. Moreover, it recites that the two primers hybridize to opposite strands. Further, it recites that the portion amplified excludes the signal peptide encoding region. Finally, it recites that the amplified coding sequence consists of nucleotides 12 to 456 of SEQ ID NO: 4. Since applicants have taught the primers of SEQ ID NO: 2 and 3 it is clear that they were in possession of primers within the scope of the claims. Those of skill in the art would readily recognize that modifications to the primers could be made, such as changing the length of the primers without affecting their function. Similarly, those of skill in the art would readily understand that minor sequence variations could be incorporated into the primers, such as adding or removing restriction sites, without adversely affecting their function. Applicants claim primers having certain recited characteristics. Those of skill in the art would readily admit that applicants were in full possession of the subject matter of claim 21 at the time of filing.

Withdrawal of this rejection to claims 1-49 is respectfully requested as each of the claims are adequately described by the specification such that those of skill in the art would recognize that applicants were in possession of what is claimed.

The Rejection of Claims 21, 23, and 24-47 under 35 U.S.C. § 112, First Paragraph

Claims 21, 23, and 24-47 have been rejected under 35 U.S.C. § 112, first paragraph, as not enabled for their full scope. The Office Action asserts that "the specification, while being enabling for a method of making an expression construct [with] using SEQ ID NO: 6, does not reasonably provide enablement for all expression constructs that produce Islet Neogenesis Associated Protein (INGAP)." Page 7, lines 14-17. The Office Action asserts that the claims of the issued patent are limited to and enabled for SEQ ID NO: 6 and 4. Page 7, lines 17-18.

The Office Action asserts the claims are not enabled for all expression constructs that produce INGAP because

> the claims are also drawn to SEQ ID NO: 4 variants which encompasses thousands of sequences. The specification does not provide any examples of methods that may be used to determine the critical percent identity that must be maintained in making these conservative substitutions and retain the desired function. The specification also does not give any guidance concerning structural or functional parameters/features that polypeptides must retain that would allow one skilled in the art to identify them as OFQ receptors.

Page 8, lines 9-15[1].

To meet the enablement requirement one reasonably skilled in the art must be able to "make or use the invention from the disclosures in the patent coupled with information known in

[1] Applicants assume that the Office Action intended to refer to INGAP instead of OFQ receptors, as OFQ receptors do not apply to the instant application.

the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 737 (Fed. Cir. 1988).

Rejected claim 21 is drawn to a pair of primers for amplifying a portion of the human INGAP coding sequence consisting of nucleotides 12 to 456 of SEQ ID NO: 4. This coding sequence excludes the nucleotides encoding the INGAP signal peptide. The primers hybridize to opposite strands of a double-stranded INGAP template. A first primer hybridizes to the 5' end of the coding sequence for mature human INGAP and the second primer hybridizes to the 3' end of the nucleotide sequence encoding mature human INGAP. One of skill in the art could make and use primers that amplify this sequence. Thus one of skill in the art could make and use the invention of claim 21 without recourse to undue experimentation.

The remaining independent claims in the rejection, 23, 29, 45, and 47, each recite an INGAP sequence for "mature human INGAP." Mature human INGAP is disclosed as nucleotides 12 to 456 of SEQ ID NO: 4 of the application. Thus one of skill in the art could make and use the claims without recourse to undue experimentation.

The specification discloses structural and functional parameters that polypeptides must retain to be identified as mature human INGAP. The specification of the instant application expressly incorporates by reference the disclosure U.S. Application Serial 08/709,662, now U.S. Patent 5,840,531 ('531 patent). The '531 patent discloses that INGAP exerts a biological effect on pancreatic ductal cells. The "biological effect of the encoded product upon pancreatic ductal cells will also serve to identify the gene as an INGAP gene." Column 7, lines 6-8. Thus an INGAP sequence is identified by its ability to exert a biologic effect on pancreatic ductal cells. INGAP was known in the prior art by virtue of WO 96/26215. Thus those of skill in the art would know how to make and use INGAP and INGAP genes.

Withdrawal of this rejection of claims 21, 23 and 24-47 is respectfully requested.

The Rejection of Claims 1-49 under 35 U.S.C. § 112, Second Paragraph

Claims 1-49 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse. The Office Action specifically asserts ten reasons why the claims stand rejected. Each will be discussed separately.

A. The Office Action asserts that claim 1 is indefinite in the recitation "INGAP activity" because the claims do not recite the "activity" of INGAP that is referred to. The Federal Circuit has established that a patent claim is sufficiently definite to satisfy the statutory requirements if one skilled in the art would understand the bounds of the claim when read in light of the specification. *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1993). The activities of INGAP are definite when read in light of the specification. The specification discloses that the activities of INGAP include induction of ductal cell proliferation and differentiation, induction of beta cell regeneration from ductal cells, induction and stimulation of islet cells to grow, and avoidance of apoptosis in ductal cells. See the specification at column 1, lines 27-28; and column 11, line 13. See also U.S. Patent 5,840,531 at column 7, lines 44-48; and column 12, lines 41-43. U.S. Patent 5,840,531 issued from Ser. No. 08/709,662 which was incorporated by reference into the specification of the instant application at column 1, lines 30-33. Withdrawal of this rejection to claim 1 is respectfully requested as the activity is clear from the specification.

The Office Action also asserts that independent claim 1 and dependent claims 13, 15-18, 29 and 48 are indefinite for reciting "amino acids 27 to 175." Claims 1, 13, 15-18, and 48 have been amended to recite "amino acid residues 27 to 175" as suggested in the Office Action to

correct the alleged ambiguity. Claim 29 has not been amended, as applicants have been unable to locate the offending phrase in the claim. Withdrawal of this rejection to claims 1, 13, 15-18, 29 and 48 is respectfully requested.

B. The Office Action asserts that claim 2 is indefinite because it is broader than the claim from which it depends, claim 1. The Office Action states "claim 1 recites 'is not present immediately 5' of said first nucleotide sequence' and claim 2 recites 'are not present 5' of said first nucleotide sequence,' and this terminology is broader." (Page 10, lines 10-11.) Claim 2 is not broader than claim 1. The full clause of claim 1 recites "wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5' of said first nucleotide sequence." The entire clause of claim 2 recites "wherein nucleotides 1-16 of SEQ ID NO: 1 are not present 5' of said first nucleotide sequence." Reading the entire phrase clarifies that "a second nucleotide sequence" that "is not present" (claim 1) is broader than the specific requirement that "nucleotides 1-16 of SEQ ID NO: 1 are not present" (claim 2). Thus claim 2 is not broader than claim 1. The Office Action similarly rejects claim 30 for broadening claim 29. For the reasons stated above, claim 30 is not broader than claim 29. Withdrawal of this rejection to claims 2 and 30 is respectfully requested.

C. The Office Action asserts that claim 6 is indefinite for reciting "promoter/operator." The Office Action alleges that "it is unclear if the slash mark refers to 'and' or 'or' (see also claims 26, 34 and 41)." (Page 10, lines 13-14.) Promoter/operator is a term of art in which the virgule means "and." One of skill in the art would recognize that the *lac* promoter/operator recited in claim 6 refers to a transcriptional control sequence naturally found in *E. coli* and would readily be able to identify its sequence. GenBank accession number X56095 teaches that a *lac* promoter/operator sequence is present at nucleotides 1 to 291 of the full-length nucleotide

sequence entry. Exhibit 1. GenBank accession number J01636 teaches a *lac* promoter/operator sequence is located at nucleotides 1146-1282 of the full-length nucleotide sequence of the entry. Exhibit 2. Exhibits 1 and 2 were each entered into GenBank prior to October 1996, the date to which priority in the instant application is claimed. Thus *lac* promoter/operator is a term that would be understood by one of skill in the art. Claims 6, 26, 34, and 41 are also clear. Withdrawal of this rejection to claims 6, 26, 34, and 41 is respectfully requested.

D. The Office Action asserts that claims 7 and 8 lack basis for "transcriptional initiation site" because the specification does not support the amendment substituting "transcriptional initiation site" for "promoter." It is not necessary for terms to be disclosed in the specification *in haec verba*. The MPEP § 2173.05(e) sets forth that:

> The mere fact that a term or phrase used in the claim has no antecedent basis in the specification disclosure does not mean, necessarily, that the term or phrase is indefinite. There is no requirement that the words in the claim must match those used in the specification disclosure.

In any event, these two terms are synonymous. The Merriam Webster's dictionary defines a promoter as "a binding site in a DNA chain at which RNA polymerase binds to initiate transcription of messenger RNA by one or more nearby structural genes." Exhibit 3, definition 4, emphasis added. Moreover, the amendment substituting "the transcriptional initiation site" for "a promoter" is supported by the specification. The specification discloses that: "For eukaryotic expression system, it is exceedingly useful to choose a promoter sequence which is capable of initiating constitutive transcription to achieve constitutive high level expression of the protein." (Column 3, lines 41-44.) A promoter sequence is described as an element that initiates constitutive transcription. Thus the promoter sequence is a transcriptional initiation site. The amendment to claim 7 is thus supported by the specification.

The amendment to claim 8 is also supported. The specification, referring to constitutive transcription initiators, discloses: "Rous sarcoma virus long terminal repeat (RSVLTR) is an example of such promoter." (Column 3, lines 45-46.) Thus the specification discloses the RSVLTR promoter as an example of a constitutive transcriptional initiator. The amendment to claim 8 is thus supported by the specification.

The Office Action also asserts that claims 7 and 8 do not limit claim 1. The Office Action cites applicants' declaration as evidence for support of this allegation because "applicant stated on the Declaration that 'claims 7 and 8 improperly refer to an additional element (a promoter sequence) which is in actuality already recited in independent claim 1 (as a transcriptional initiation site); therefore the promoter sequence is not an additional element.'" (Page 11, lines 2-5.) The declaration, however, stated only that "a promoter sequence" is not an additional element because it is not different than "a transcriptional initiator." It did not make any assertion about other recitations such as "constitutive" and "RSVLTR" which limit claims 7 and 8, respectively, with regard to claim 1. Therefore, claims 7 and 8 do limit claim 1. Claim 1 recites that a first nucleotide sequence is "operably linked to a transcriptional initiation site and a translational initiation site." Claim 7 limits claim 1 by requiring that "the transcriptional initiation site is capable of initiating constitutive transcription." Claim 8 further limits claim 7 because it requires that "the transcriptional initiation site is Rous sarcoma virus long terminal repeat." Thus claims 7 and 8 are narrower in scope than claim 1. Withdrawal of this rejection to claims 7 and 8 is respectfully requested.

E. The Office Action asserts: "Claim 10 is indefinite for the recitation of EBNA-1 without the corresponding spelled out meaning (see also claim 38)." (Page 11, lines 9-10.) Claims 10

and 31 have been amended to recite the words corresponding to the acronym EBNA-1. Withdrawal of this rejection to claims 10 and 31 is respectfully requested.

F. The Office Action asserts that claim 13 is indefinite for reciting "INGAP protein." The Office Action asserts that "'INGAP' is sufficient as it means 'islet cell neogenesis associated protein.'" (Page 11, lines 12-13.) Claims 13, 14, 45 and 46 have been amended to "INGAP" at each instance of "INGAP protein." Withdrawal of this rejection is respectfully requested.

G. The Office Action asserts that claims 6, 19, 26, 34, and 41-44 are indefinite in the recitation of "transcription initiation site." The Office Action asserts that these claims "lack antecedent basis for 'transcription initiation site' as the disclosure of the patent in column 2, lines 42-45 state that 'suitable inducible transcription initiators include the lac promoter/operator, the tac promoter, the trp promoter, the λcI promoter, the tet promoter, as well as others which are known in the art." (Page 11, lines 16-19.) This quotation supports the recitation of "transcription initiation site" in the rejected claims. The transcription initiators described are promoters. Promoters are the sites at which transcription is initiated. See Exhibit 3, definition 4. Thus the passage supports "transcription initiation site" in the claims. Any ambiguity or inconsistency introduced by column 2, lines 42-45 is not apparent. Withdrawal of this rejection to claims 6, 19, 26, 34, and 41-44 is respectfully requested.

H. The Office Action asserts that claim 21 is indefinite over the use of "hybridizes." The Office Action alleges hybridizes is not definite "without providing the hybridization conditions." (Page 12, line 2.) "Hybridizes" is clear and no reasons have been provided why it is not clear on its face.

The Office Action also asserts that claim 21 is also indefinite because no sequence is recited; "there is no recitation of a sequence in the claim (see also claims 23-47)." The claims as

amended are clear with regard to the sequence of mature human INGAP recited in the claims, *i.e.* nucleotides 12 to 456 of SEQ ID NO: 4. Thus the claims are definite. Withdrawal of this rejection to claim 21 and also claims 23-47 is respectfully requested.

The Office Action further asserts that claim 21 and 27 are indefinite because they recite "a portion of the human INGAP" and "there is no indicia of the size/length of the portion (see also claim 27)." (Page 12, lines 4-5.) Claims 21 and 27, however, actually define the size of the portion of human INGAP. Claims 21 and 27 each recite "mature human INGAP consisting of nucleotides 12 to 456 of SEQ ID NO: 4" and "said portion excludes the nucleotides encoding the signal peptide." Claims 21 and 27 clearly recite the length of the portion. Withdrawal of this rejection is respectfully requested.

I. The Office Action also asserts that claim 49 is indefinite for reciting "SEQ ID NO.:2." Claim 49 has been amended to recite "SEQ ID NO: 2." Thus the rejection is rendered moot. Withdrawal of the rejection to claim 49 is respectfully requested.

J. The Office Action has also rejected claim 23 as indefinite for reciting "forming/form" rather than "making/make." Claim 23 has been amended as suggested in the Office Action because the terms seem equivalent. Thus the rejection is rendered moot. Withdrawal of this rejection to claim 23 is respectfully requested.

Provisional Double Patenting Rejection of Claims 1-49

Claims 1-49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 09/717,095. Applicants respectfully traverse.

The Office Action asserts that the claimed subject matter is an obvious variation of the claims in copending Application No. 09/717,095 because

> claims in the present application are directed to a recombinant construct for expression of INGAP which comprises a nucleotide sequence that encodes the amino acids set forth in SEQ ID NO: 6. Note that the copending application is directed to an isolated DNA molecule which encodes an INGAP protein set forth in SEQ ID NO: 2 and both sequences are identical with the exception of one residue (SEQ ID NO: 6 has an additional Methionine in the beginning of the sequence).

Page 13, lines 10-15. Independent claims 1, 13, 15, 21, 23, 29, 45, and 47 of the instant reissue application all require that the encoded INGAP sequence lack a signal sequence. They are not an obvious variation of the subject matter claimed in U.S. Ser. No. 09/717,095. Each of independent claims 1, 13, and 15 recites "encoding amino acid residues 27 to 175 as shown in SEQ ID NO: 6" and "wherein a second nucleotide sequence encoding a signal peptide is not present immediately 5' of said first nucleotide sequence." Independent claim 21 recites a first primer which "hybridizes to the 5' end of the coding sequence for mature INGAP" and "wherein said portion excludes the nucleotides encoding the signal sequence." Independent claim 23 recites "a coding sequence for mature human INGAP" and "which is devoid of the signal sequence of the coding sequence of INGAP." Independent claims 29, 45, and 47 each recites a "sequence encoding mature human INGAP" and "a signal peptide according to SEQ ID NO: 5 is not present immediately 5' of said first nucleotide sequence." Thus each of the claims of the instant application requires that the INGAP sequence lack the signal sequence. The claims of U.S. Application No. 09/717,095 do not mention the signal sequence or teach the desirability of excluding it. Thus the claims of the subject reissue application are not obvious over the claims of 09/717,095 as alleged by the Patent Office.

The specification of the instant application discloses that despite prior knowledge of the coding sequence of INGAP, attempts to express INGAP at high levels were unsuccessful. Column 1, lines 33-38. The instant inventors discovered that deleting the signal sequence of INGAP allowed them to express INGAP at high levels. It was not obvious that exclusion of the signal sequence of INGAP from the full-length INGAP sequence would result in increased expression. The claims of U.S. Application No. 09/717,095 do not teach or suggest such a result.

The Office Action also asserts that the claims drawn to a pair of oligonucleotide primers (claims 21-22 and 49) are obvious over the claims of U.S. Ser. No. 09/717,095. The Office Action alleges that "the present application and copending application both claim probes, primers and have claims directed to antisense strands which would render each other obvious." (Page 13, lines 16-18.) The present application, however, does not claim probes or antisense strands. Independent claim 21 and dependent claims 22 and 49 are drawn to a pair of oligonucleotide primers for amplifying a portion of the human INGAP coding sequence. Copending U.S. Ser. No. 09/717,095 does not claim a pair of primers. Pairs of oligonucleotide primers are distinct from a probe or an antisense construct. Therefore the rejection of claims 21-22 and 49 should be withdrawn as based on an incorrect premise. Moreover, the probes and antisense construct of U.S. Ser. No. 09/717,095 do not teach or suggest primers which amplify mature INGAP, *i.e.*, exclude the signal sequence.

Independent claim 23 and dependent claims 24-28 and 48 are drawn to methods of making an expression construct. U.S. Ser. No. 09/717,095 has no claims related to such methods. Moreover, the expression construct expresses mature INGAP, *i.e.*, excludes the signal. None of the claims of U.S. Ser. No. 09/717,095 teach or suggest this subject matter. Thus the methods of claims 23, 24-28 and 48 are distinct from the claims of U.S. Ser. No. 09/717,095 and

are not obvious variants. Therefore, the rejection of claims 23-28 and 48 should also be withdrawn.

Double Patenting Rejection of Claims 1-49

Claims 1-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,840,531. Applicants respectfully traverse.

U.S. Patent 5,840,531 is the patent for which U.S. Ser. No. 09/717,095 requests reissue. For the same reasons stated above, the double patenting rejection of 1-49 of the instant application should be withdrawn. The claims of the instant, later priority date, application could not have been filed with the claims of U.S. Patent 5,840,531 because the invention was not made at the time of filing the application which matured into the '531 patent. Moreover, the instant invention was not disclosed in the applications which became the '531 patent.

Respectfully submitted,

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Status of Claims and Support for Claim Changes

Status of Claims

Patent claims 1-18 and newly added claims 19-49 are pending in the application.

Support for Claim Changes

Claims 1, 13, 15-18, and 48 have each been amended to recite "amino acid residues 27 to 175" in place of "amino acids 27 to 175." Support for this amendment can be found in the specification were it is disclosed that: "The coding sequence of amino acid residues 27-175 of INGAP protein are included in the constructs." (Column 3, lines 8-9.) The amendment is supported by the specification, clarifies the claims and does not narrow the scope of the claims.

Claim 7 has been amended to recite "wherein the transcriptional initiation site is capable of initiating constitutive transcription" in place of "further comprising a promoter sequence capable of initiating constitutive transcription." The amendment is supported by the specification where it is disclosed that "it is exceedingly useful to choose a promoter sequence which is capable of initiating constitutive transcription to achieve constitutive high level expression of the protein." (Column 3, line 42-44.) Thus the specification supports that the transcriptional initiation site referred to in independent claim 1 is capable of initiating constitutive transcription. The amendment is supported by the specification, and does not narrow the scope of the claims.

Claim 8 has been amended to recite "the transcriptional initiation site is Rous sarcoma virus long terminal repeat" in place of "the promoter sequence is Rous sarcoma virus long terminal repeat." The specification provides support for this amendment where it describes

sequences that are useful for causing constitutive transcription. The specification discloses that: "Rous sarcoma virus long terminal repeat (RSVLTR) is an example of such promoter." (Column 3, lines 45-46.) Thus the specification describes that the RSVLTR provides constitutive transcription and supports the amendment to the claim. The amendment clarifies the claim and does not narrow the scope of the claim.

Claims 10 and 38 have been amended to recite "Epstein-Barr nuclear antigen-1 (EBNA-1)" in place of "EBNA-1." The amendment merely clarifies the claim by providing the spelled-out meaning of the well-known acronym EBNA-1. This amendment also merely clarifies the claim and does not narrow the scope of the claim.

Claims 13, 14, 45, and 46 have also been amended to recite "INGAP" in place of "INGAP protein." The amendment merely clarifies the claim such that it does not recite "islet cell neogenesis protein protein." The amendment also does not narrow the scope of the claim.

Claim 13 has amended to recite "transcriptional" in place of "transriptional." The amendment merely corrects the spelling of transcriptional in the claim. Thus the amendment clarifies the claim and does not narrow the scope of the claim.

Claims 21, 23, 27, 29, 45 have been amended to recite that the portion of the human INGAP coding sequence or the coding sequence for mature human INGAP consists of nucleotides 12 to 456 of SEQ ID NO: 4. The amendment is supported by claim 16. Claim 16 recites that the nucleotide sequence encoding amino acids 27-175 of INGAP comprises nucleotides 12-456 of SEQ ID NO: 4. The specification discloses that the signal sequence of INGAP "comprises amino acids 1 to 26." Thus nucleotides 12-456 of SEQ ID NO: 4 encode INGAP without the signal sequence. The amendment introduces no new matter.